INTER-RELATIONS OF THE VOLUME AND TIMING COMPONENTS OF VENTILATION DURING CARBON DIOXIDE REBREATHING IN AWAKE AND ANAESTHETIZED SUBJECTS

N. W. GOODMAN AND A. M. S. BLACK

The volume and timing components of ventilation are usually measured as the tidal volume and the ventilatory rate, other ventilatory variables being derived from these. Ventilatory rate is estimated normally by counting over a number of breaths. The product of tidal volume and rate over a number of breaths is the ventilation over those breaths. The duration of the total respiratory cycle can be measured for a single breath; it is the reciprocal of the ventilatory rate for that single breath, the breath-by-breath frequency (f). The product of breath-by-breath f and breath-by-breath VT is the breath-by-breath minute ventilation, VT. The total respiratory cycle (Tc) is made up of the inspiratory period (Ti) and the expiratory period (Te). The quotient VT/Ti is the mean inspiratory flow rate (which will be termed IF and not VT in this paper, to avoid confusion with VT).

Anaesthetists are used to considering some of these variables more or less formally when selecting an artificial ventilator, and adjusting it to control the ventilation of their patients. Respiratory physiologists use them formally and in more detail for describing spontaneous ventilation in conscious subjects and anaesthetized animals, but their application to spontaneously breathing anaesthetized patients has so far been relatively limited (Derenne et al., 1978; Gautier, 1980).

The breath-to-breath variability that occurs during spontaneous ventilation cannot occur during artificial ventilation because the variables are preset by the anaesthetist. This paper is concerned with the inter-relations of the variabili-

SUMMARY

We studied the relations between the volume and timing components of ventilation during carbon dioxide rebreathing in conscious subjects and patients anaesthetized with propofol. In conscious responses, breath-by-breath minute ventilation (VT) generally correlated better with end-tidal carbon dioxide than did tidal volume (VT), but VT correlated better than VT in the anaesthetized responses. The source of this difference was that, whereas VT and the inspiratory period were both smaller and less variable when subjects were anaesthetized rather than conscious, the expiratory period was no less variable, and this disturbed the usual inverse relation between VT and the duration of the ventilatory cycle. Anaesthesia stabilized the switch from inspiration to expiration, but not that from expiration to inspiration. In some patients, it produced a disturbance pronounced enough to suggest bimodality of the timing of expiration.
response of tidal volume. We have made a preliminary report of our findings (Goodman and Black, 1986).

SUBJECTS, PATIENTS AND METHODS

Subjects and patients

Our results were from ventilatory responses to carbon dioxide obtained from 10 healthy awake volunteers and 12 patients anaesthetised with propofol. Eight of the volunteers were about to embark on a Himalayan expedition, and recording their ventilatory responses to carbon dioxide was part of an investigation of the causes of mountain sickness. The 12 patients (five male) were aged 22–64 yr and weighed 53–96 kg. All gave informed consent to the study, which was approved by the Hospital Ethics Committee. All were unpremedicated and had subarachnoid anaesthesia. General anaesthesia was maintained by an infusion of propofol alone while the subject breathed 100% oxygen via a face mask held carefully to avoid any leakage or entrainment (Goodman, Carter and Black, 1987). The ventilatory responses to carbon dioxide were tested at least once at one or both of two infusion rates of propofol: 100 or 200 µg kg\(^{-1}\) min\(^{-1}\). Eight of the patients returned subsequently to have their responses tested when conscious.

Apparatus and data collection

The apparatus for the rebreathing manoeuvre (Read, 1967) was as described and used by Goodman, Carter and Black (1987). The principle is that a linearly increasing carbon dioxide stimulus is presented to the respiratory centres by having the subject rebreathe to and from a closed system while the response of ventilation is recorded. Although most of the data were obtained during ventilatory responses to an increasing carbon dioxide tension, non-stressed steady-state breathing was also recorded in a few patients. The same rebreathing apparatus was used, but it was primed with 100% oxygen and had a carbon dioxide absorber in the circuit to prevent the increase in carbon dioxide tension. The Fi\(_{O_2}\) was greater than 60% for all of the recording periods.

Signals of end-tidal carbon dioxide tension (PE\(_{CO_2}\)) and tidal volume passed to a two-channel pen recorder (running paper speed 25 mm min\(^{-1}\)) and thence to an Apple IIe microcomputer for storage and analysis. Digital values of PE\(_{CO_2}\), tidal volume (VT), inspiratory time (TI) and expiratory time (TE) together with calibration values of PCO\(_2\) and volume were stored on disc. The absolute limits of accuracy with our settings for the computer's analogue-to-digital convertor were 0.043% for carbon dioxide and 17 ml for volume. The program loop for collecting data ran at 30 Hz exactly, so timings were accurate to approximately 33 ms. Sighs and other very obviously abnormal breaths were deleted before analysis. We did not use a formal statistical test to reject these outliers, but did so from a visual inspection of the scatter plots. It was very unusual to have to reject more than two outliers from any particular response.

Statistical analysis

Regressions. The analysis was based on linear least squares regressions, the regression process being used in different ways for different purposes.

Regressions of PE\(_{CO_2}\) on time could be done to check the linearity of the increase in carbon dioxide tension during the response. The response of ventilation to carbon dioxide was obtained by regressing breath-by-breath ventilation (VT) on PE\(_{CO_2}\); the tidal volume response to carbon dioxide was obtained by regressing VT on PE\(_{CO_2}\). The response of ventilatory rate (f) to carbon dioxide was obtained by regressing f on PE\(_{CO_2}\).

Regressions on elapsed time were performed for all the measured variables VT, f, TI, TE, and the derived variables VT and VT, and the derived variables VT and VT. The particular interest, for all the variables, was in their variability about any linear trend with time. We took the correlation coefficient (r) as the initial index of variability and investigated the variability further by examining the "time residuals".

Time residuals. The time residual of a variable for a particular breath is the difference between its measured value for that breath and the value indicated by the regression line of best fit to elapsed time. This is illustrated in figure 1 for VT-time residuals and f-time residuals from a rebreathing manoeuvre in a conscious subject: the time residuals are the vertical lines joining the breath-by-breath data points to the line of best fit. The breath-by-breath time residuals were calculated for all the measured and derived variables except VT, and stored on computer disc.

The time residuals were used in three ways: (i) Time sequence plots were examined visually for indications of major non-linearity during the response. Formal statistical tests were not applied (Draper and Smith, 1981).
Fig. 1. Carbon dioxide rebreathing in a conscious subject: upper graph breath-by-breath tidal volume (VT) plotted against elapsed time; lower graph breath-by-breath ventilatory frequency (f) plotted against elapsed time. r = Correlation coefficient from least squares linear regression. The vertical lines joining the data points to the line of best fit are the “time residuals”. In general, for each breath, larger-than-zero VT-time residuals (+) occur with smaller-than-zero f-time residuals (−) and vice versa (e.g. thick vertical lines at approximately 110 and 180 s), but this relation is not universal (e.g. thick lines at approximately 30 s).

(ii) The residual standard deviation (RSD), the square root of the averaged sum of squares of the residuals, was used as a measure of the overall variability of the ventilatory variable about its trend. If there is no trend, the RSD is the same as the standard deviation of the variable about its mean value.

(iii) The breath-by-breath residuals of one ventilatory variable about its trend were correlated with the breath-by-breath residuals for another to see how much of the about-trend variability of the first variable was related to that of the second. We were particularly interested in possible relations between the about-trend variabilities of VT, f, Tt and Te.

Other statistical procedures

The Fisher z-transformation was used to average correlation coefficients (Documenta Geigy, 1970). The Wilcoxon test for pair differences was used to compare groups of correlation coefficients for different ventilatory variables within the same responses, and to make within-patient comparisons in those eight patients from whom measurements were made in both the conscious and the anaesthetized states.

RESULTS

The first rebreathing manoeuvre from each conscious subject or patient was usually disturbed by unfamiliarity and other distractions of consciousness; it was used as practice, and the results were discarded. It was usually followed by two further responses which were technically satisfactory. All “anaesthetized” responses were analysed, provided that there were no obvious technical faults (Rebuck, 1976). In all we collected 19 satisfactory ventilatory responses to carbon dioxide from 10 volunteer subjects. Eight of the patients provided 13 responses when conscious and 15 while anaesthetized, and the remaining four patients were studied only when anaesthetized and provided eight responses. Thus there were 32

Table I. Mean correlation coefficients (after z-transformation) of various variables, and their residuals against time, during carbon dioxide rebreathing awake and anaesthetized. VT = breath-by-breath minute ventilation; VT = tidal volume; IF = mean inspiratory flow, f = ventilatory frequency, Tt = inspiratory time; Te = expiratory time. The correlation coefficients at levels of significance corresponding to 32 degrees of freedom are also shown.

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Anaesthesia</th>
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<tbody>
<tr>
<td>No. subjects</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>No. responses</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Mean No. breaths</td>
<td>34.8</td>
<td>34.0</td>
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<tr>
<td>Correlation v. Pco2</td>
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<tr>
<td>VT</td>
<td>0.933</td>
<td>0.891</td>
</tr>
<tr>
<td>VT</td>
<td>0.826</td>
<td>0.914</td>
</tr>
<tr>
<td>IF</td>
<td>0.940</td>
<td>0.919</td>
</tr>
<tr>
<td>VT-resid. v. f-resid.</td>
<td>−0.526</td>
<td>−0.219</td>
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<td>VT-resid. v. Ti-resid.</td>
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<td>0.411</td>
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<tr>
<td>VT-resid. v. Te-resid.</td>
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<td>0.102</td>
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<tr>
<td>Ti-resid. v. Te-resid.</td>
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<td>r for P &lt; 0.05</td>
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<td>P &lt; 0.01</td>
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<tr>
<td>P &lt; 0.001</td>
<td>0.539</td>
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"conscious" and 23 "anaesthetized" carbon dioxide responses (table I).

The numbers of breaths in each response ranged from 23 to 55, the mean and range being similar for conscious and anaesthetized responses. Most of the responses looked linear on superficial inspection.

Responses of ventilatory rate to carbon dioxide rebreathing

There was a significant positive correlation between frequency and \( Pe'_{CO_2} \) in 25 of the 32 awake responses, but in none of the anaesthetized responses. Even with a strong correlation, the actual increase in frequency was small.

Comparisons of variability around \( V_I \) and \( V_T \) responses to carbon dioxide

In 26 of the 32 conscious responses, the ventilatory response to carbon dioxide (\( V_I v. Pe'_{CO_2} \)) had a higher correlation coefficient than did the tidal volume response to carbon dioxide (\( V_T v. Pe'_{CO_2} \)). Correspondingly, the mean correlation coefficient (after \( z \)-transformation) for the \( V_I \) responses was 0.933 compared with 0.891 for the \( V_T \) responses. Under anaesthesia, the opposite was true. In 20 of the 23 anaesthetized responses, the \( V_T \) response showed a higher correlation coefficient than did the \( V_I \) response; the mean correlation coefficient of the \( V_T \) responses was 0.914, compared with 0.826 for the \( V_I \) responses (table I).

These differences were tested formally for the eight patients who provided both conscious and anaesthetized responses. During consciousness the \( V_I \) responses adhered to the line of best fit significantly better than did the \( V_T \) responses; and during anaesthesia they did so significantly less well (\( P < 0.05 \), Wilcoxon).

It is worth remarking that IF usually correlated with \( Pe'_{CO_2} \) at least as well as the better of \( V_I \) or \( V_T \) — that is the correlation tended to be as good as that of \( V_I \) in the awake state, and as \( V_T \) in the anaesthetized state.

Correlations between carbon dioxide and elapsed time

Regressions of \( Pe'_{CO_2} \) with time, when performed, showed correlation coefficients very close to unity unless there were technical problems such as leaks at the mouth. In valid responses, any deviations from the lines of best fit were mainly caused by errors in the \( Pe'_{CO_2} \) signal arising from the relatively limited precision of measurement, and from any difference between the recorded \( Pe'_{CO_2} \) and the actual central carbon dioxide stimulus to ventilation at that moment. We removed this variability by regressing the ventilatory variables on time rather than on \( Pe'_{CO_2} \); the fit of the trend with time was always better than the fit of the trend with \( Pe'_{CO_2} \). Consequently, when examining the variability of any time or volume component of ventilation about its trend, we always examined the variability about the trend with time: the time residuals.

Correlations of \( V_T \) residuals with \( f, T_I \) and \( T_E \) residuals

\( V_T \) and \( f \). There was a striking difference between conscious and anaesthetized responses (table I). Twenty-six of the 32 conscious responses showed significant (\( P < 0.05 \)) negative correlations between the two sets of residuals. Significant negative correlations (< 0.05) were found in only 11 of the 23 anaesthetized responses. Correspondingly, the average correlation coefficient for the \( V_T \) residuals against \( f \) residuals was \( -0.526 \) in the conscious responses and \( -0.219 \) in the anaesthetized responses (table I).

An inverse correlation between \( V_T \) and \( f \) implies a direct correlation between \( V_T \) and \( T_{\text{tot}} \), and this was indeed the case.

\( V_T, T_I \) and \( T_E \). The major contribution to the direct \( V_T \)-to-\( T_{\text{tot}} \) relationship in both the awake and anaesthetized state was from that between \( V_T \) residuals and \( T_I \) residuals. This relationship was stronger in the conscious state; correlations significant at \( P < 0.05 \) were more frequent, and the averaged correlation coefficient was greater than while anaesthetized (table I). The correlations between \( V_T \) and \( T_E \) residuals were weaker and significant less frequently, especially under anaesthesia.

Overall there was no correlation between \( T_I \) and the actual increase in frequency was small.
residuals and $T\theta$ residuals, although correlation from eight conscious and two anaesthetized responses achieved significance. There was no association between those responses showing a significant correlation with those showing a relatively brisk response of ventilatory frequency during rebreathing.

**The RSD of the ventilatory variables**

The RSD is an index of the absolute variability about any trend during the response. It is useful to scale it somehow to the value of the variable itself. This we did crudely by relating it to the average value of the variable over the first five breaths of rebreathing, before it was too much affected by any trend. The quotient of the RSD and the mean value for each variable has some similarities to a coefficient of variation. It will be termed "CV," and is expressed as a percentage in table III.

Table III shows that the main differences between the state of consciousness and the state of anaesthesia with propofol are decreases in $VT$ and $T_i$, with an appreciable reduction in the variability of each about any trend they might show during a response. $IF$ also decreases, as does its variability (not shown in table).

**Time sequence plots**

On visual inspection, the scatter of tidal volume and frequency residuals about their respective trends was usually symmetrical, with a range of variation that did not alter from the beginning to the end of the response. The exceptions were examined in detail, and gave us two types of information.

**NL1: Non-linearity consistent with a tidal volume limitation.** In one response from one conscious subject, the time sequence plot of $VT$ was obviously convex upwards, which was consistent with the tidal volume response to carbon dioxide being less steep at the end of the response. Ventilatory rate increased during the response, but there was no marked non-linearity. The correlation of $VT$ with $P_{e}CO_2$ (or time) was stronger than the correlation of $VT$ with $P_{e}CO_2$ (or time), and there was a weak but significant negative correlation between the $VT$–time residuals and the $f$–time residuals.

A second-order polynomial regression gave a better fit between $VT$ and time, and the residuals from this regression gave a much stronger negative correlation between the $VT$ and the $f$ residuals than there was for the residuals from the linear fit.
NL2: Cyclic non-linearity. The \( V_t \)-time residuals and the \( f \)-time residuals from two of the anaesthetized responses seemed to cycle together around the zero line of their time sequence plots. Both of these responses gave positive correlations between the \( V_t \)-time and \( f \)-time residuals, and one of these correlations was significant. Second- or third-order polynomial fits of both \( V_t \) with time and \( f \) with time were marked improvements on the corresponding linear fits, and the positive correlation between the \( V_t \)-time and \( f \)-time residuals was lost.

BM: Bimodality of ventilatory timing. One patient showed marked bimodality of ventilatory timing when anaesthetized, but not when conscious. All three of his anaesthetized responses gave plots of \( V_t \) against \( P_{\text{ET}}\text{CO}_2 \) that could not be fitted by a single straight line, although plots of \( V_t \) against \( P_{\text{ET}}\text{CO}_2 \) could (fig. 2). On the paper recording of his ventilation during the operation, there seemed to be two populations of breaths: they had cycle lengths of either about 3.5 s or about 4.5 s. This bimodality was best seen in a plot of \( T_{\text{TOT}} \) against elapsed time during a period of steady-state ventilation. In figure 3, \( T_{\text{TOT}} \) is divided into \( T_I \) and \( T_E \) and shows that the bimodality of \( T_{\text{TOT}} \) is caused apparently entirely by a bimodality in \( T_E \).

There was a suggestion of bimodality in anaesthetized carbon dioxide responses from some of the other patients, but none was so obvious.

**DISCUSSION**

**Ventilatory patterns during steady-state breathing**

When ventilatory drive increases from one steady-state level to another, ventilation increases because of increases in both the average tidal volume and the average frequency. With carbon dioxide breathing, the \( V_t \) effects predominate until \( V_t \) approaches one-third to one-half of vital capacity (Hey et al., 1966; Clark and Von Euler, 1972; Gardner, 1977); after this point increases in
f make an increasing contribution. Increases in average Vt are brought about mainly by increases in average inspiratory flow over an unchanged or somewhat shortened average inspiratory time. Any increases in average f are brought about mainly by a reduction in average expiratory time (Kay, Strange Petersen and Vejby-Christensen, 1975; Newsom Davis and Stagg, 1975; Gardner, 1980). Thus if larger breaths are to be expired in a shorter time, the expirations are likely to need extra contributions from the expiratory muscles. These relationships between the average values of VT and f in different steady-states must be distinguished from the relationships between the variabilities about those average values at any particular level of ventilatory drive.

When ventilatory drive is steady, mean inspiratory flow remains relatively steady from breath to breath (Priban, 1963; Newsom Davis and Stagg, 1975). Variations about the average Ti produce corresponding variations about the average Vt, as if the inspiratory phase is controlled in the mode of a constant flow generator with variable time cycling. (The reality is, of course, more complex: the inspiratory muscles generate a negative inspiratory pressure, and the inspiratory flow is not constant, but has a time profile determined by the resistance and compliance of the ventilatory system.) Longer than average inspirations result in larger than average breaths, and these in turn tend to be followed by longer than average expirations. (This implies that the expiration of the larger breaths is not assisted by any extra expiratory muscle force, and that the lung volume must return to FRC before the next inspiration can begin.) The net result of the variations in Ti and Tex is an inverse relationship between breath-by-breath variations in Vt and f, which acts as a simple "mechanical" within-breath self-regulating process tending to smooth out the breath-by-breath minute ventilation. This inverse relation between the variabilities of Vt and f is the converse of the relation between their average values at different, steady-state, levels of ventilatory drive.

During longer periods of undisturbed breathing, ventilation tends to oscillate around its mean steady-state level. There may be a number of superimposed oscillations with periods of a few minutes to an hour or so and, during such oscillations, Vt and f are as likely as not to be changing together. This probably reflects the operation of a number of between-breaths self-regulating processes as they "hunt" around a level of ventilatory drive appropriate to the level of metabolic activity. The underlying mechanism for this is more complex and involves central nervous processes which may be susceptible to change by anaesthesia.

Ventilatory patterns during steadily increasing drive

This study shows that many of the features of ventilatory pattern during different steady states of ventilatory drive apply also during the dynamic state when there is a constantly increasing ventilatory drive. When studying variability in the steady-state, one looks at the deviations of the ventilatory variables from their steady-state means. In this study, because the variables themselves were changing, we looked at the deviations from the trend, while the variable changed during a carbon dioxide rebreathing response. As with the discussion of ventilatory patterns in different steady states, one must distinguish between associations between trends and associations of variability about trends. For the rest of this discussion we shall be interested primarily in association between the about-trend variabilities.

For most responses a linear regression (Read, 1967) was perfectly adequate to establish the trend, that is the gradient of the line, and we used the correlation coefficient (r) as an index of variability about the trend, that is closeness of fit of a particular variable over the course of a response. Our use of correlation coefficients, rather than any other derived statistic, as our index of comparison of variability is valid, because comparisons were made within individual responses for the same breaths, and hence for identical numbers of degrees of freedom. It was coincidence that the mean number of breaths per response was similar for the conscious and anaesthetized responses, and this made some of the comparisons easier.

We observed that Vt followed its trend better than Vt during consciousness, but worse during anaesthesia. Vt and Vt are linked by a factor −f, the ventilatory frequency — so it is necessary to consider what relationship between them can be responsible for this observation. The first possibility to consider is that non-linearities of the Vt or Vr response to carbon dioxide may be responsible, and that the observation may be an artefact of applying linear regression analysis...
to non-linear processes. In a previous study (Goodman and Curnow, 1985), we applied polynomial regressions to ventilatory responses to carbon dioxide, and could thereby identify significant non-linearities when the original plots of $V_t$ against $P_F CO_2$ looked acceptably linear; however, the actual improvement in regression fit was usually marginal. In this study we applied polynomial fits only when our previous experience indicated that there was something to be gained from it.

If the ventilatory frequency is absolutely constant throughout a response, the $V_t$ response is identical to the $V_T$ response, except that $f$ acts as a universal scaling factor. The gradient of the $V_t$ response is then the product of $f$ and the gradient of the $V_T$ response. The correlation coefficients of the two responses must then be identical.

If $V_T$ and $f$ both increase linearly during a response, then the scaling factor is also increasing, and the response of ventilation will then be non-linear. It will increase more steeply at the end of the response than at the beginning. For this reason, a linear fit to the $V_t$ response might yield a poorer correlation coefficient than a linear fit to the $V_T$ response. However, even when a trend in $f$ was seen, the actual change was small, and the resulting non-linearity was not very obvious; besides, increases in $f$ only occurred in conscious patients, and in them $V_t$ followed its trend better than $V_T$ — and did so irrespective of whether there had been a change in $f$.

In some circumstances, the increase in tidal volume might not be progressive throughout the carbon dioxide response, but might show a break point at some limit of tidal volume. The continuing increase in ventilatory drive might then be expressed as an increased $f$ after the break point: the combination of the two non-linearities might then yield a linear ventilatory response to carbon dioxide and a better linear fit for breath-by-breath $V_t$ than for breath-by-breath $V_T$.

A marked effect of this sort was found in only one response, from a conscious patient (see Results, time sequence plots, NL 1). When both $V_t$ and $V_T$ were fitted by polynomial regressions, the fit to the breath-by-breath $V_t$ was still better than the fit to $V_T$, and the negative correlation between $V_T$-time residuals and $f$-time residuals was stronger.

Thus non-linearities do not have a significant part to play in explaining our results.

Even if the ventilatory frequency does not increase, or decrease, consistently during a response, there will inevitably be breath-by-breath variation in $f$ (and its reciprocal $T^{out}$). If there were no relation at all between the variabilities about trend of $V_T$ and $f$, the general expectation would be that the about-trend variability of the product $V_t$ of the variables $V_T$ and $f$ should be greater than the variability of either $V_T$ or $f$. The situation seen in conscious patients is the opposite of this. It is the negative correlation between the about-trend variabilities of $V_T$ and $f$ which offers the most likely explanation for this exception to the general expectation.

The simple mechanical within-breath self-regulating mechanism which holds ventilation to its mean value during the steady state also holds it to its trend during dynamic changes of ventilatory drive. It appears to be less effective during anaesthesia than during consciousness, and the reasons for this need some consideration.

There are three sources of about-trend variability of $V_T$, $T_i$, and $T_e$. There is a contribution to real variability that is related to real variability in one or both of the others; there are contributions of real variability which are not related to real variability in the others; and there are contributions of variability which are related to errors of measurement. The size and significance of the correlation coefficients between the residuals of the different variables reflect the relative size of the first of these contributions.

During consciousness, the real about-trend variability of $T_i$ is appreciable. It makes an important contribution to the about-trend variability of $V_T$ when compared with the contributions of variability in mean inspiratory flow and the measurement errors in both $V_T$ and $T_i$. Under anaesthesia, IF is less variable about its trend, $T_i$ is also less variable as well as being shorter; $V_T$ is less variable and smaller. The absolute measurement errors in $V_T$ and $T_i$ remain the same, so that they contribute relatively more to the total measured about-trend variabilities of $V_T$ and $T_i$. Thus the $V_T$-to-$T_i$ correlation is weaker under anaesthesia than during consciousness.

Similar considerations apply during the expiratory phase, but there is another important effect. During consciousness, the size of a particular breath tends to make some contribution to the duration of its expiration: lung volume takes longer than trend to return to FRC after tidal volumes that are bigger than trend, and the
system seems to wait for the return to FRC before initiating the next inspiration. Thus the real, related variabilities of $T_i$, $V_T$ and $T_E$ make an appreciable contribution to their total measured variabilities. However, the effect does not appear to be as strong as during steady-state breathing and, under anaesthesia, it practically disappears.

This seems to be caused by the effect of propofol anaesthesia on the central clock-and-switch mechanisms which govern the changes between inspiration and expiration. The inspiratory phase is strikingly shortened. (It may be that the reduced variability can be explained by the absence of the distractions to which the conscious mind is susceptible.) However, the expiratory phase remains just as long and just as variable as during consciousness. Because of the shorter inspiration at reduced inspiratory flow, the tidal volume is smaller, and this tidal volume can always be expired in well under the time allowed by the timer for the expiratory phase. There tends to be a much more pronounced expiratory pause than during consciousness, and presumably the next inspiration is started by the central expiratory timer later than would be expected if it were simply a matter of having to wait for lung volume to return to FRC. In one clear case (see Results, time sequence plots, BM) the effect was more complex. Under propofol anaesthesia the expiratory clock changed abruptly and apparently randomly between one expiratory timing and another.

**Limitations of method**

During awake carbon dioxide responses, subjects and patients breathed through a mouthpiece; during anaesthetized responses patients breathed through a face mask. This may have altered the frequency and tidal volume of resting ventilation, but we do not think it influenced our analysis. Newsom Davis and Stagg (1975) used a face mask, and our analysis of the variabilities from stressed breathing are in agreement with theirs from the steady state. We do not know what contribution there may have been from the stimulus of holding a mask tightly to the face of our anaesthetized patients. We would have expected it to cause marked irregularities of both frequency and tidal volume, and perhaps marked non-linearities during rebreathing, but these were not seen.

Nor do we think that differences in the mean values of ventilatory variables between the awake and anaesthetized states were of much influence. The biggest differences were the larger tidal volumes when awake, and the smaller and slower increase in $P_{E'CO}$ during the anaesthetized responses. However, the differences in pattern were present also in those records of steady-state breathing that we looked at, not just during rebreathing.

On-line data collection and computer analysis are not necessary if all one wants to know is the ventilatory sensitivity to carbon dioxide, although it certainly eases the analysis, and the programs were written for this purpose. They are, however, the only feasible way of investigating breath-by-breath ventilatory patterns, but the questions raised in this study have stretched our present measuring capabilities and our programs to the limit of their useful accuracy (Newsom Davis and Stagg, 1975). For instance, the program measures time with a loop lasting 33 ms; this is accurate enough to calculate a simple ventilatory response, but we must expect a minimal error of about 1% in a $T_{tot}$ of 3 s, 3% in a $T_i$ of 1 s, and 30% or more in a $T_i$ residual of 0.1 s or less.

We have been careful to avoid spurious correlations when dealing with derived variables. For instance, IF residuals showed significant negative correlations with $T_i$ residuals in a number of responses. If this were real, it would suggest that there was a volume-limiting control — that is that faster breaths are also shorter, so that the final tidal volume is the same as with slower breaths because slower breaths are longer. The more likely explanation, however, is that the measurement errors in the $T_i$ residuals have simply been regressed on their inverse, which is contained in the quotient $V_T/T_i$.

Such spurious correlations will not arise for measurements which are truly independent. The relatively limited resolving power of our present measuring capabilities leads us to expect that the estimates of significance which have emerged from our correlations are minimal estimates of the true strength of the relationships, and that when we pursue the investigation with improved equipment, more interesting relationships are likely to emerge. Because of the objectives and design of our algorithms for data collection, we were unable to study the inspiratory and expiratory flow profiles in detail. In particular, we could not measure accurately any inspiratory or expiratory pauses, although we were confident in our overall timings of inspiration and expiration.
Between-breaths self-regulating processes

We have concluded that the simple "mechanical" within-breaths self-regulating process which has been described for steady-state breathing operates also during the rebreathing manoeuvre although it is weakened during propofol anaesthesia by some interference with inspiratory and expiratory timing. There was no sign in conscious patients of any longer-term variation about the response trend. Perhaps when the ventilatory system is attempting to catch up with a progressively increasing drive, there is no opportunity for any "hunting" behaviour. The simultaneous variations of $VT$ and $f$ about the response trend (Results, time sequence plots, NL2) may be an indication of such behaviour under anaesthesia, and two other anaesthetized responses from other patients were somewhat similar. However, these patients also gave other responses which did not show these features; they may simply have resulted from variations in arousal during relatively light anaesthesia.

Ventilatory responses to carbon dioxide by rebreathing do not last long enough to study the longer-term variations in the volume and timing components of ventilation, and they remain to be studied in steady-state breathing in anaesthetized man.

ACKNOWLEDGEMENTS

We are grateful to ICI for supplies of propofol and to our subjects and patients for their time.

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